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RAS blockade: new possibilities in the treatment of complications of diabetes

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Diabetic nephropathy is the main cause of end stage renal disease both in the USA and in Europe. In addition, the development of diabetic nephropathy greatly increases the cardiovascular risk in these patients. Studies performed with angiotensin converting enzyme (ACE) inhibitors have shown that blockade of the actions of angiotensin II (AII) is the treatment of choice for diabetic patients who have developed microalbuminuria.

ACE inhibitors and AT_1 inhibitors

Studies demonstrating the positive effects of ACE inhibitors have all shown that these drugs are able to decrease the risk of nephropathy, once chronic failure is present, by 50%. It is hoped that a new way of blocking the effects of angiotensin II could decrease the risk even further. Interest has particularly focused on the emerging role of the angiotensin II receptor antagonists.

MECHANISM OF ACTION

Distribution of the ACE and angiotensin II type I (AT_1) receptor in the kidney is very different. ACE is mostly found in the medulla, while AT_1 receptors are present in the inner medulla and the cortex. This contrasting distribution could mean that blockade of each could achieve different renal effects.

With an ACE inhibitor, there is decreased stimulation of the AT_1 receptor because less angiotensin II is formed and therefore less is available to bind with the receptor. In contrast, an AT_1 antagonist binds to the receptor and occupies the position that angiotensin II would normally have. By impairing the binding of angiotensin II in this way, there is a more complete blockade of the effects of AII (table 1).

When an AT_1 antagonist is administered there is an increase in angiotensin II, which then binds to the AT_2 receptor. Available data suggest that this is a positive attribute of AT_1 antagonists. With an ACE inhibitor, of course, there is no such increase in AII concentration.

Changes in plasma renin activity are similar with the two types of drug. However, with ACE inhibitors the half life of kinase is prolonged. With AT_1 receptor antagonists, the stimulation of AII produces an increase in nitric oxide production, which is mediated by kinase, but there is no increase in the concentrations of kinase.

Table 1 Pharmacological effects of AT_1 receptor antagonists and ACE inhibitors

	AT_1 receptor antagonists	*ACE inhibitors*
AT_1 stimulation	↓↓	↓
AT_2 stimulation	↑	↓
Plasma renin activity	↑	↑
Angiotensin II concentrations	↑	↓
Bradykinin concentrations	=	↑

In animal studies, when concentrations of angiotensin II are increased by administering an AT_1 receptor antagonist, the stimulation of the AT_2 receptor produces an antiproliferative, antifibrotic, and apoptotic effect.[1] These actions oppose the negative effects of angiotensin II mediated through the stimulation of the AT_1 receptor.

In human studies, the administration of candesartan produces a decrease in filtration fraction which represents the amount of plasma that is filtered through the glomerular.[2] This means that the effects of angiotensin II in the efferent artery are being blocked, thereby decreasing intraglomerular pressure.

In addition, the antiproteinuric capacity of AT_1 antagonists has been widely proved. The classic study exploring this process showed that there was a titration dependent antiproteinuric effect with the AT_1 receptor antagonist losartan, which was not seen with the ACE inhibitor enalapril.[3] The ability of the two drugs to decrease proteinuria appears to be similar. However, if the drugs are used in combination, there is an additive effect. Therefore the two drugs may be causing a drop in proteinuria by different mechanisms.

In addition, both ACE inhibitors and AT_1 antagonists have been shown to decrease microalbuminuria in type 2 diabetes.

RENAL VASODILATION

Can these two classes of drug be differentiated in terms of their capacity to block the renal effects of angiotensin II? It has been shown that blockade of the renin-angiotensin system is accompanied by a striking renal vasodilatory response.[4] Moreover, the renin-angiotensin system can be blocked at many different levels.

For example, ACE inhibitors have been shown to increase renal plasma flow by approximately 100 ml/minute.[5] Interestingly, the use of a renin inhibitor increases flow to approximately 150 ml/minute. Renovasodilation is therefore more pronounced with a renin inhibitor. When AT_1 antagonists have been compared with ACE inhibitors, their ability to vasodilate the kidney is higher and therefore the blockade of the effects of angiotensin II must be greater.[6]

PREVENTION OF DIABETIC NEPHROPATHY

Are these newer drugs of value in preventing diabetic nephropathy and slowing the progression of diabetic nephropathy? There are two large ongoing studies that will look at both the

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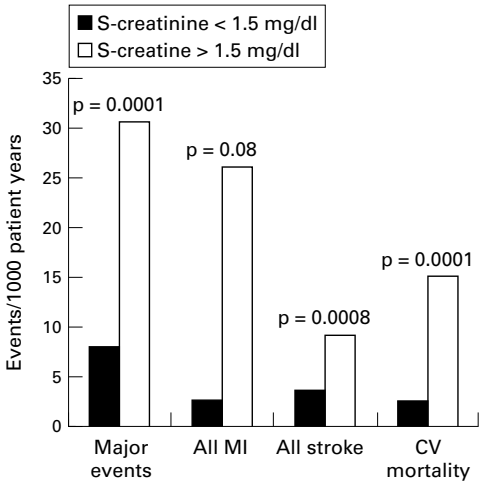

Figure 1 Rate of cardiac events in relation to creatinine concentrations at baseline.

renal and cardiovascular outcome of treating diabetic patients with AT_1 receptor antagonists

RENAAL study

In the double blind RENAAL study a group of 1500 type 2 diabetics have been randomised to losartan, with titration to 50 mg, 100 mg, and then a diuretic is added, or placebo. Placebo is defined as good blood pressure control obtained with an antihypertensive agent that does not block the renin-angiotensin system.

IDNT study

In the IDNT study 1650 patients with type 2 diabetes and hypertension have been randomised to double blind treatment with irbesartan, amlodipine or placebo—that is, target blood pressure achieved with an antihypertensives other than a calcium channel blocker, ACE inhibitor or AT_1 antagonist.[7 8] It will determine the efficacy of irbesartan in reducing the rate of progression of renal disease and its adverse clinical sequelae including cardiovascular disease.

These two ongoing studies are of particular interest as cardiovascular disease is extremely prevalent in diabetic patients. The incidence of cardiovascular disease is particularly high whenever renal damage is present.

This can be illustrated by data from the HOT study, which showed that whenever there was a decrease in renal function, the prevalence of major cardiovascular events (myocardial infarction, stroke or cardiovascular mortality) increased (fig 1).[9] The kidney and the cardiovascular system are at an increased risk when renal function is impaired. This means that blockade of angiotensin II not only protects the kidney but may also protect the heart.

METABOLIC CONTROL

It is important that any drug given to a diabetic patient is neutral in terms of glycaemic control. Importantly, it has been shown that glycaemic control in type 2 diabetics did not change when candesartan was administered for 12 weeks. The lipid profile was also not affected.[10]

SERUM POTASSIUM

A recent study looked at the changes in serum potassium in hypertensive patients with nephropathy following the administration of an ACE inhibitor or an AT_1 antagonist.[11] As expected, there was a significant increase in serum potassium following the administration of the ACE inhibitor. Importantly, this was not seen following the administration of an AT_1 receptor antagonist. This suggests that the risk of developing hyperkalaemia is less with AT_1 receptor antagonists than with ACE inhibitors.

Treatment guidelines

The control of blood pressure in diabetes is difficult and may require multiple drugs. For example, in the UKPDS more than two drugs were required in almost one third of patients.[12] Also, in the HOT study 50% of patients presented with systolic pressures above 140 mm Hg.[9]

Treatment should be started as soon as possible. The Joint National Committee VI guidelines states that treatment should be started as soon as blood pressure is above 130/85 mm Hg.[13] The World Health Organization/International Society of Hypertension guidelines advise starting treatment as soon as blood pressure is above 140/90 mm Hg.[14] The goal of blood pressure control is 130/85 mm Hg. This limit is even lower if there is microalbuminuria present in a diabetic. Microalbuminuria correlates closely with many of the other well known risk factors for cardiovascular events and death. Importantly, microalbuminuria has been shown to correlate with left ventricular hypertrophy, which is associated with a very poor prognosis.

In the future one of the aims of management will be to start treatment earlier. In this way such large reductions in blood pressure will not be required and it is more likely that monotherapy will be sufficient in some patients. Many patients will, of course, still require three or more drugs to achieve adequate blood pressure lowering.

Conclusion

There is a need for drugs with blood pressure independent effects such as a reducing microalbuminuria and proteinuria. Up until recently, the only drugs to have achieved this were ACE inhibitors. Recent data, however, suggest that AT_1 antagonists are at least as effective as ACE inhibitors but act through a different mechanism of action. In certain circumstances, it may be beneficial for both drugs to be used in combination.

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Trial acronyms
IDNT: Irbesartan Diabetic Nephropathy Trial
HOT: Hypertension Optimal Treatment
RENAAL: Reduction of Endpoints in NIDDM with the AIIA Antagonist Losartan
UKPDS: United Kingdom Prospective Diabetes Study

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